

NOTES

HYPERSENSITIVITY REACTIONS: MULTIPLE MECHANISMS

GENERALLY, WHAT ARE THEY?

PATHOLOGY & CAUSES

- **Hypersensitivity (intolerance):** undesirable reactions produced by immune system (e.g. allergies, autoimmunity)
- Range from minor (e.g. swelling, itching) to tissue-damaging, fatal
- Multiple mechanisms indicates the presence of two or more of the four types of hypersensitivity reaction
 - **Type I:** allergy, acute hypersensitivity
 - **Type II:** antibody-dependent cytotoxicity
 - **Type III:** immune complex disease
 - **Type IV:** delayed type hypersensitivity/ cell-mediated immune memory response
 - **Tissue specific antibody response:** autoimmune disease/organ rejection

Common Hypersensitivity reactions with multiple mechanisms

- Hypersensitivity pneumonitis
- Transplant rejection
- Latex allergy (I+IV)
- Sjögren syndrome
- Autoimmune hepatitis Autoimmune polyendocrine syndrome (APS1, APS2)
- Autoimmune adrenalitis
- Systemic autoimmune disease

SIGNS & SYMPTOMS

- Non-specific flu-like symptoms (e.g. fever, chills, malaise, cough, joint pains)
- Multiple mechanisms varies by location; see individual disorders

DIAGNOSIS

LAB RESULTS

- **Acute (Type I) hypersensitivity**
 - Spirometry/pulmonary function, skin tests (exposure to specific allergens provokes skin reaction), radioallergosorbent tests (quantify allergen specific IgE levels)
- **Type II–IV hypersensitivity**
 - Identify organ/cell component specific antibodies

Biopsy (Type II–IV hypersensitivity)

- Immune cell infiltration of organ
- Compromise of normal organ anatomy

TREATMENT

MEDICATIONS

Acute (Type I) hypersensitivity

- **General**
 - Withdraw offending agent, H1 receptor blockers
- **Anaphylaxis**
 - **Hypertension:** epinephrine, intravenous fluids, vasopressors (e.g. dopamine)
 - **Bronchoconstriction:** nebulized B2 agonists (e.g. salbutamol)
 - Late-phase reaction, corticosteroids

Type II–IV hypersensitivity

- Immunosuppression

SURGERY

Type II–IV hypersensitivity

- Irreversible organ damage/rejection → transplant of new organ

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OTHER INTERVENTIONS

Type II–IV hypersensitivity

- Support organ function

HYPERSENSITIVITY PNEUMONITIS

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PATHOLOGY & CAUSES

- AKA (extrinsic) allergic alveolitis
- **Reaction to antigens** usually 1–5 micrometers in size; fungal, bacterial, mycobacterial, animal, chemical sources
 - **Type III** (antibody complex mediated) and **IV** hypersensitivity (delayed cell-mediated)
 - Inhaled antigen → forms haptens → inflammation of alveoli, small distal airways within lung
 - **Histological changes:** inflammation of bronchi, peribronchiolar tissue; diffuse interstitial inflammatory infiltrate; poorly defined granulomas, associated giant cells within lung interstitium/alveoli
 - Long-standing disease → pulmonary fibrosis, emphysematous changes → ↓ lung capacity, alveolar gas exchange → hypoxemia
- > 200 common causative agents identified, often given eponymous names (e.g. farmer's lung, bird fancier's lung, etc.)

RISK FACTORS

- **Farming**, ventilation, water-related exposure; poultry, **bird handling**; veterinary work, animal handling; grain, flour processing; grain dust; mold contamination; milling, construction; plastic manufacturing; painting; electronics industry, other chemical industries; textile workers

SIGNS & SYMPTOMS

Acute

- Fever, chills, malaise, **cough**, **chest tightness**, **dyspnea**, rash, **headache**
- Resolves 12 hours to several days after cessation of exposure

Sub-acute

- Productive cough, dyspnea, fatigue, anorexia, weight loss, pleurisy, mild hypoxemia
- Lesser severity, longer duration
- Resolves weeks to months after cessation of exposure

Chronic

- Insidious onset cough, progressive dyspnea, fatigue, weight loss, clubbing, tachypnea, respiratory distress, inspiratory crackles (lower lung fields)
- Emphysematous component
- May have irreversible component, even if antigen removed

DIAGNOSIS

DIAGNOSTIC IMAGING

Bronchoscopy/bronchoalveolar lavage

- Marked lymphocytosis; ↑ IgG, IgA, IgM

Chest X-ray

- Subacute hypersensitivity
 - Micronodular/reticular opacification in middle to lower lung zones
- Chronic hypersensitivity
 - Progressive fibrotic changes, loss of lung volume (esp. upper lobes)

High-resolution chest CT scan

- Subacute hypersensitivity
 - Diffuse micronodules, ground-glass opacification, focal air trapping/emphysematous changes, mild fibrosis
- Chronic hypersensitivity
 - Interstitial inflammation, alveolar destruction, dense fibrosis, features of emphysema (centrilobular nodules), ground glass opacification, subpleural honeycombing

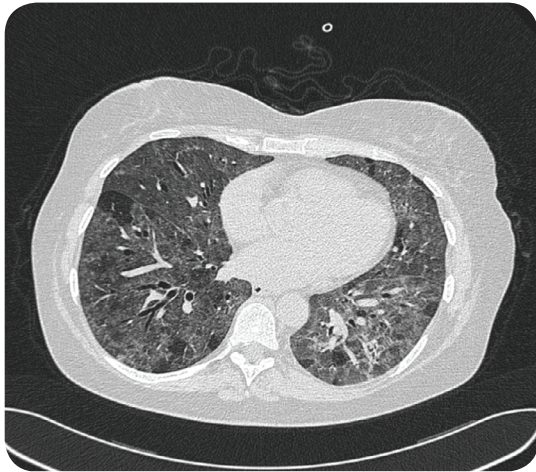


Figure 33.1 A high resolution CT scan in the axial plane of an individual with hypersensitivity pneumonitis. There are multiple centrilobular ground glass nodules and anterior subpleural reticulation.

LAB RESULTS

- Lung biopsy
 - Loose, poorly-defined noncaseating granulomas in vicinity of small airways
 - Focal fibrotic changes
- Immunoassay
 - Detect antibodies against specific antigens
 - Chemical labels accumulate in response to specific antigen-antibody reactions/enzymes bind to specific markers → catalyze color-changing reaction
 - **Known antigens:** identify specific antibodies in blood sample

OTHER DIAGNOSTICS**Diagnostic criteria: acute hypersensitivity**

- **Definite hypersensitivity pneumonitis:** 2 and 3, plus one other
 - **Probable disease:** 1, 2A, 3
 - **Subclinical disease:** 1, 3A
 - **Previous sensitization:** 1 only
1. Known exposure
 - History of exposure
 - Aerobiological/microbiological investigation of environment → confirmed exposure
 - Specific IgG antibodies against identified antigen
 2. Compatible clinical, radiographic, physiologic evidence
 - **Respiratory signs:** crackles, weight loss, cough, breathlessness, fever, wheezing fatigue, esp. hours after exposure
 - **Radiographic:** reticular, nodular, ground glass pattern
 - **Lung function:** spirometry (restrictive, obstructive, mixed); diffusion capacity for carbon monoxide (reduced, altered gas exchange)
 3. Bronchoalveolar lavage
 - Lymphocytosis
 - Positive specific immune response to antigen
 4. Inhalation challenge testing
 - Worsening clinical condition after exposure to environment
 - Worsening clinical condition after exposure to specific antigen in hospital setting
 5. Histopathology
 - Poorly formed noncaseating granulomas
 - Mononuclear cell infiltrate

Lung function

- Subacute
 - Restrictive pattern
- Chronic
 - Restrictive pattern, hypoxemia at rest, desaturates with exercise, ↓ carbon monoxide diffusion capacity

TREATMENT

MEDICATIONS

- Glucocorticoids
 - Subacute, chronic hypersensitivity
- Immunosuppression
 - Refractory disease

SURGERY

- Lung transplant
 - Advanced chronic lung disease

OTHER INTERVENTIONS

- Identify allergen, **reduce/eliminate exposure** → disease generally self-limiting (if acute)
- Occupational measures
 - Reduce antigenic burden, moisture control, ventilation, personal protective devices (respirator masks)

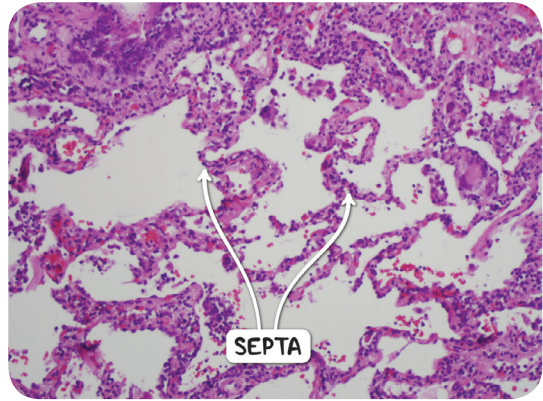


Figure 33.2 A section of the lung of an individual with hypersensitivity pneumonitis. The alveolar septa are thickened and contain numerous lymphocytes.

TRANSPLANT REJECTION

osms.it/transplant-rejection

PATHOLOGY & CAUSES

- Transplanted tissue rejected (attacked) by new host's immune system → destruction of transplanted tissue

Timescale of rejection

- **Hyperacute rejection**
 - **Minutes** after transplant
 - Initiated by humoral immunity
 - If tissue left implanted → systemic inflammatory response syndrome
 - Often caused by **preexisting anti-human leukocyte antibodies** (HLA)
- **Acute rejection**
 - Highest risk window **one week to three months** after transplant
 - Mediated by cellular immunity
 - Occurs in nearly all transplants if **recipient inadequately immunosuppressed**

- Highly vascularised tissue (e.g. kidney, liver) esp. vulnerable
- Can be treated prior to organ failure; multiple episodes → chronic rejection

Chronic rejection

- **Months to years** after transplantation
- Fibrosis of blood vessels → long term loss of function in transplanted organs

Multiple divisions of immune system involved in rejection

- Innate immunity → attraction, activation of phagocytes
- Humoral immunity → activation of B cells → antibody secretion
- Adaptive response → cellular immunity → killer T cells induce apoptosis

Cellular markers influencing rejection

- Blood group, major histocompatibility (MHC) antigens
 - Most intense graft rejection reactions

- (hyperacute rejection) occur due to differences between donor, recipient ABO blood-groups, MHC antigens
- Blood-group antigens expressed on red blood, epithelial, endothelial cells → donor, recipient must be ABO compatible
 - Minor blood group exposure (e.g. Kell antigen) following allogeneic blood transfusion/trauma during pregnancy may also prime recipient's humoral immunity against future transplants
 - MHC compatibility assessed via molecular assay using sequence-specific primers ("tissue typing") → determination of which HLA alleles expressed by donor, recipient
 - Presence of preformed antibodies to HLA alloantigens must be evaluated to reduce risk of rejection
 - Minor histocompatibility locus
 - Short variable proteins, 9–12 amino acids in length, bound to MHC class I, II proteins
 - Provoke less vigorous immune response, may still lead to slow graft rejection
 - Potential for graft rejection even if ABO, MHC antigens match
 - Donor cell debris
 - Damage-associated molecular patterns by pattern recognition receptors (e.g. toll-like receptors on phagocytes) → further secretion of proinflammatory cytokines, phagocyte chemotaxis

COMPATIBILITY OF MAJOR BLOOD GROUP ANTIGENS

BLOOD GROUP	ANTIGENS	ANTIBODIES	CAN GIVE BLOOD (RBC) TO	CAN RECEIVE BLOOD (RBC) FROM
AB	A and B	None	AB	AB, A, B, O
A	A	B	A and AB	A and O
B	B	A	B and AB	B and O
O	None	A and B	AB, A, B, O	O

STAGING

- Of acute graft rejection

Sensitization

- Recipient antigen-reactive lymphocytes proliferate in response to alloantigens on graft
- Dendritic cells migrate to peripheral lymphoid tissue → present donor's "self" peptides to recipient's lymphocytes → presentation of antigen to T cells (helper, killer subclasses), B cells → specific immunity directed at donor self peptides/
- donor major histocompatibility complex/ both
- CD4+ (T helper), CD8+ (T killer) T cells recognize alloantigen (major, minor histocompatibility complex) on foreign graft cells → proliferation
 - **Direct presentation:** donor MHC directly recognised as foreign
 - **Indirect presentation:** donor peptides residing in cleft of recipient MHC recognised
- T helper (Th) cells activate when they interact with antigen presenting cells

(APCs) that express appropriate antigenic-ligand/MHC-molecule complex, provide costimulatory signal

- Dendritic cells found in most tissue, express high levels of class II MHC → activated dendritic cells mediate direct presentation in grafts/draining lymph nodes
- APCs of host origin migrate into grafts, endocytose foreign alloantigens → indirect presentation of alloantigen
- Langerhans, endothelial cells present alloantigen to recipient's immune system

Effector phase

- Influx of immune cells into graft
- **Most common rejection mechanism:** cell mediated immunity
- **Less common:** antibody-mediated complement lysis, antibody-dependent cell-mediated cytotoxicity
- Th cell cytokines play central role → Th1 cells secrete interleukin (IL) 2, interferon (IFN) gamma → T cell proliferation, delayed type hypersensitivity response, IgG synthesis by B cells → complement activation
- Cytokines → increased expression of MHC class I, II; IFN, tumor necrosis factor (TNF)
- Elevated levels of IL-4, 5, 13, 17 → B-cell activation, eosinophil accumulation within grafts
- Antibody-mediated rejection
 - Antibodies directed against donor HLA molecules/endothelial antigens
 - Dependent on T cell maintenance of alloreactive B cells → antibody production → activation of complement, deposition of C4d among cells lining graft capillaries

TYPES

Autograft

- Transplant of "self" tissue; surplus tissue that can regenerate/tissue moved from one site to another (e.g. skin, ligament grafts)

Isograft

- Transplant of tissue between two genetic identical members of same species (e.g.

transplant between two identical twins)

Allograft

- Transfer of tissue between genetically non-identical members of same species; non-identical grafts recognised by immune system, destroyed

Xenograft

- Transplant from one member of species to another (e.g. porcine heart valve transplant)

SIGNS & SYMPTOMS

- Fever, chills, dizziness, nausea, malaise, night sweats
- Specific to transplanted organ: failure of associated organ

DIAGNOSIS

LAB RESULTS

Tissue biopsy

- T cell infiltration, accompanied by eosinophils, plasma cells, neutrophils
- Structural compromise of tissue anatomy
- Blood vessel injury

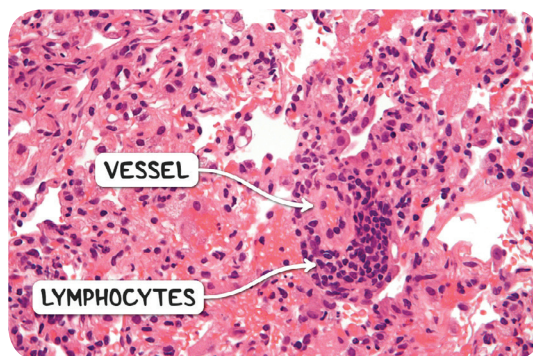


Figure 33.3 A biopsy from a transplanted lung showing a prominent perivascular lymphocytic infiltrate, consistent with rejection. There are numerous background macrophages and eosinophils.

TREATMENT

MEDICATIONS

Generalized immunosuppression

- Mitotic inhibitors (antiproliferatives)
 - Suppression of B, T cell proliferation; antimetabolites, DNA alkylating agents, fungal metabolites (also suppress T-cell cytokine expression)
- Corticosteroids
 - Anti-inflammatory, potent immunosuppressives at higher doses

Specific immunosuppression

- Targeted to specific antigens
- Monoclonal antibodies
 - Soluble ligands, bind specific cell-surface molecules → can be used to deplete recipient of particular cell population/block specific steps in cellular signalling
 - Modern monoclonal antibodies carry toxins (e.g. diphtheria) → target cell internalizes toxin → cell death
 - Cellular markers expressed only by activated T cells kill cell lines activated after transplant
 - Cytokines targeted as well; neutralized cytokine no longer stimulates target (e.g. costimulatory signals needed to activate T-helper cells)

For acute rejection

- Extensive immunosuppressive regimens: corticosteroids, calcineurin inhibitors, antiproliferatives, mTOR inhibitors
- Antibody-based treatment
 - Monoclonal anti-IL-2R alpha receptor antibodies (e.g. basiliximab), polyclonal anti-T cell antibodies (e.g. antithymocyte globulin, antilymphocyte globulin), monoclonal anti-CD20 antibodies (e.g. rituximab)

SURGERY

- Removal of transplanted tissue (hyperacute rejection)
- Bone marrow transplant (acute rejection)
 - Recipient bone marrow replaced with donor marrow; risk of graft vs host disease
- New transplant (chronic rejection)

OTHER INTERVENTIONS

- Prevent rejection
 - Total lymphoid irradiation; X-rays eliminate lymphocytes prior to transplant (e.g. bone marrow transplantation)